

What are good drug targets and how to find them?

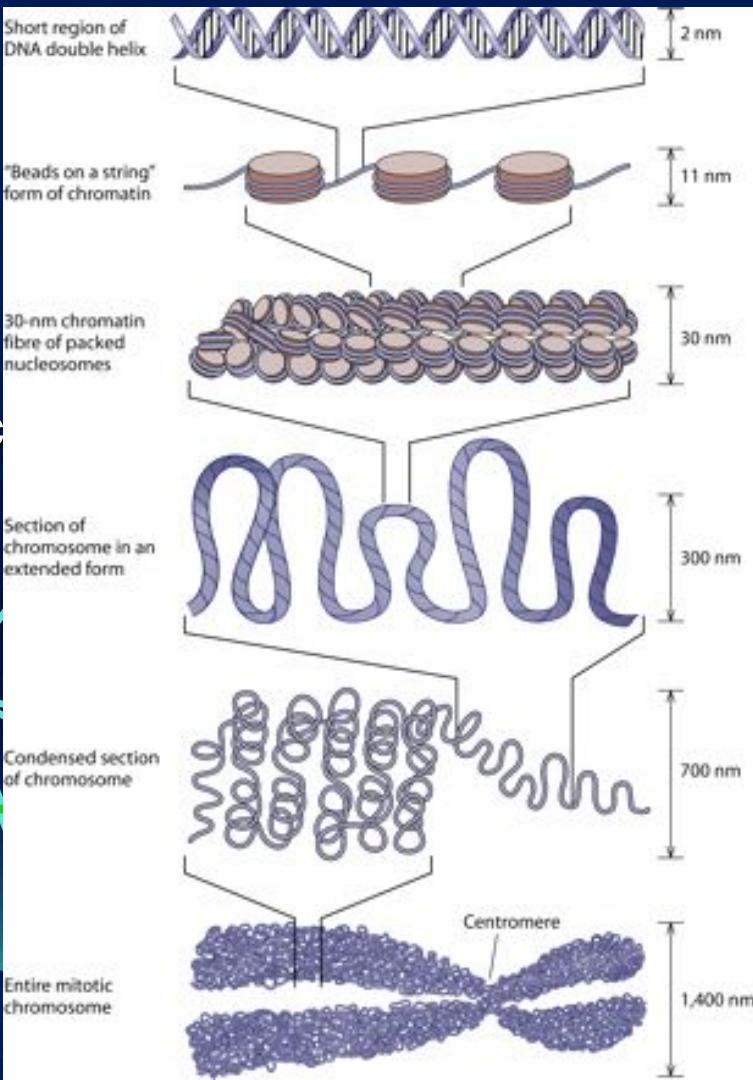
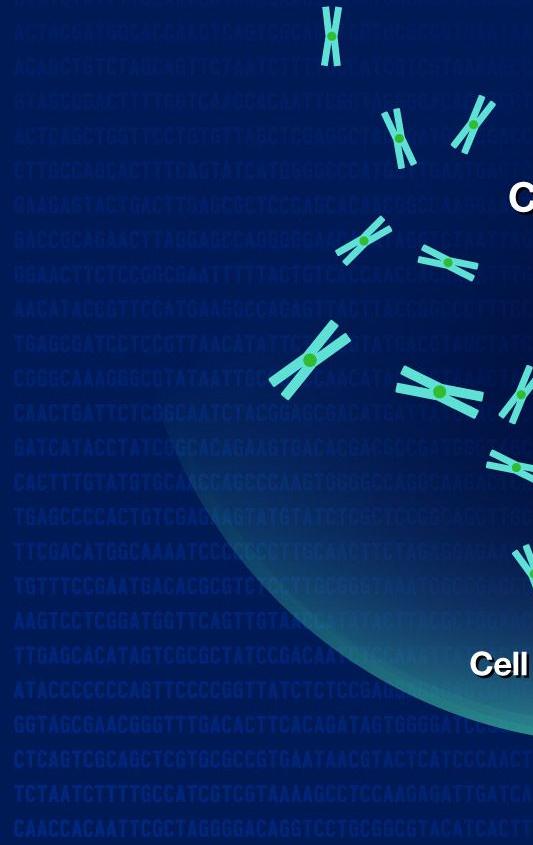
*Mathematical and Computational Biology in Drug
Discovery (MCBDD), Module I*

Dr. Jitao David Zhang, March 2021

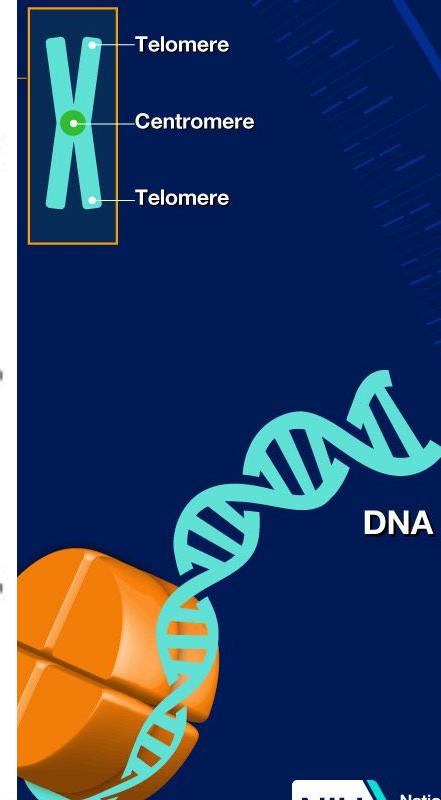
Q&A

- **Can genetics explain differences of numbers of infection and death caused by SARS-CoV-2 between countries?**
- **How much does genotyping cost? If we sequence each individual on the planet, do we solve the problem of target identification and drug discovery?**
- **Why we are so bad at selecting drug targets? Any hope that we can do it better?**
- **Any more questions?**

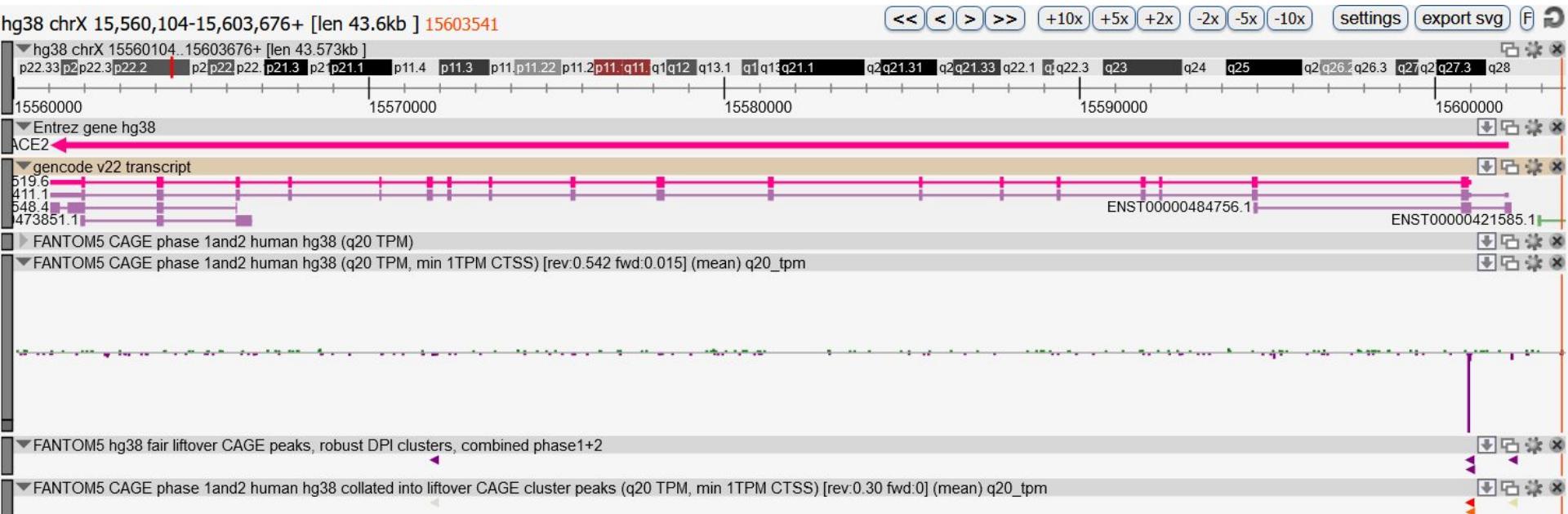
Chromosome



NHGRI FACT SHEETS
genome.gov



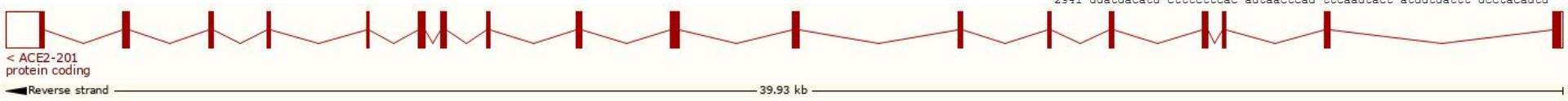
Gene structure and gene expression



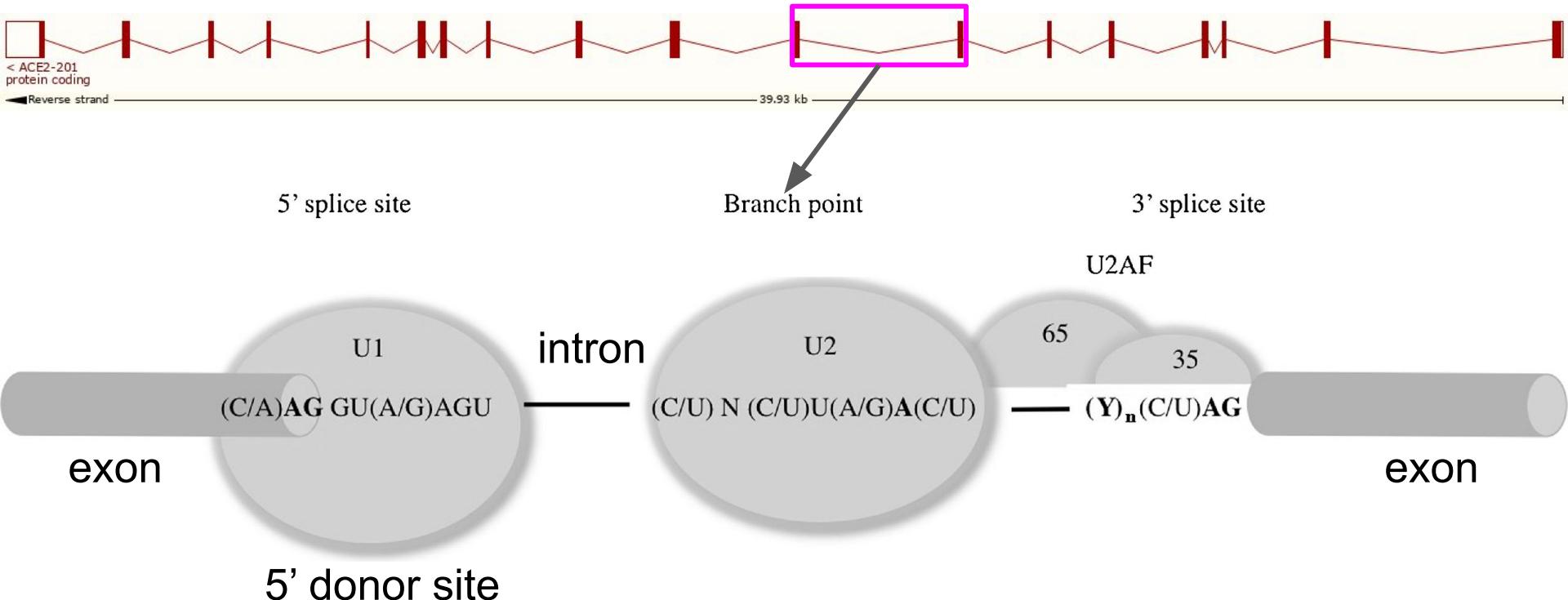
ACE2 viewed in FANTOM5/ZENBU

A mRNA of ACE2

- RefSeq record NM_001371415.1
 - EnsEMBL record
ENST00000252519.8
 - Red and blue boxes: start codon (ATG) and stop codon (TAG). The region between them is called the *coding sequence* (CDS).



The splicing code



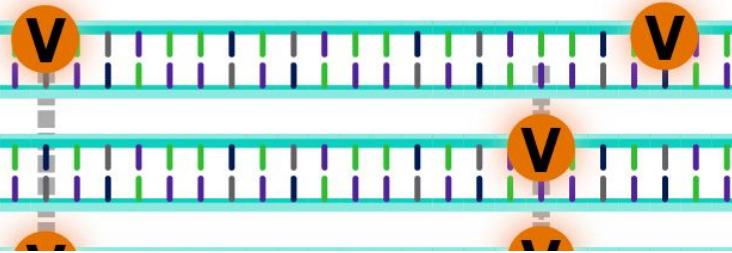
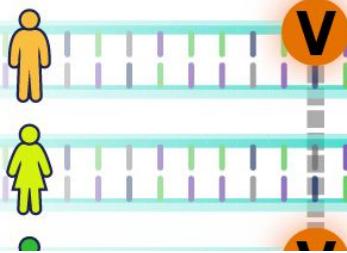


Person one

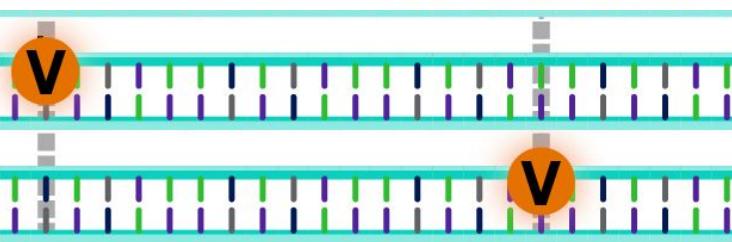
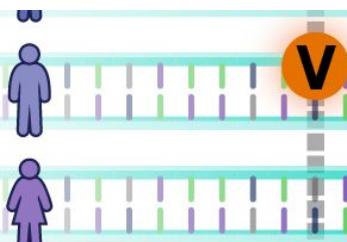
A G A C G C T

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
17-7579017-C-T	E	c.74+22G>A	● intron		Likely benign		1
17-7579831-C-T	E	c.74+8G>A	● splice region		Likely benign		1
17-7579924-G-A	E G	c.-12C>T	● 5' UTR		Likely benign		7
17-7579932-G-C	E	c.-20C>G	● 5' UTR		Likely benign		2
17-7578142-C-A	E G	c.672+35G>T	● intron		not provided		9
17-7577142-C-A	E	p.Gly266Ter	● stop gained		Pathogenic		1
17-7578188-C-A	E	p.Glu221Ter	● stop gained		Pathogenic		1
17-7578263-G-A	E	p.Arg196Ter	● stop gained		Pathogenic		1
17-7576928-TAGGAA...	E	c.920-14_920-3delTGC...	● splice region		Uncertain significance		2
17-7578171-C-A	E G	c.672+6G>T	● splice region		Uncertain significance		2
17-7578171-C-T	E	c.672+6G>A	● splice region		Uncertain significance		1
17-7579934-C-T	G	c.-22G>A	● 5' UTR		Uncertain significance		1
17-7565206-T-A	G	c.*51A>T †	● 3' UTR				1
17-7565222-C-T	G	c.*35G>A †	● 3' UTR				1

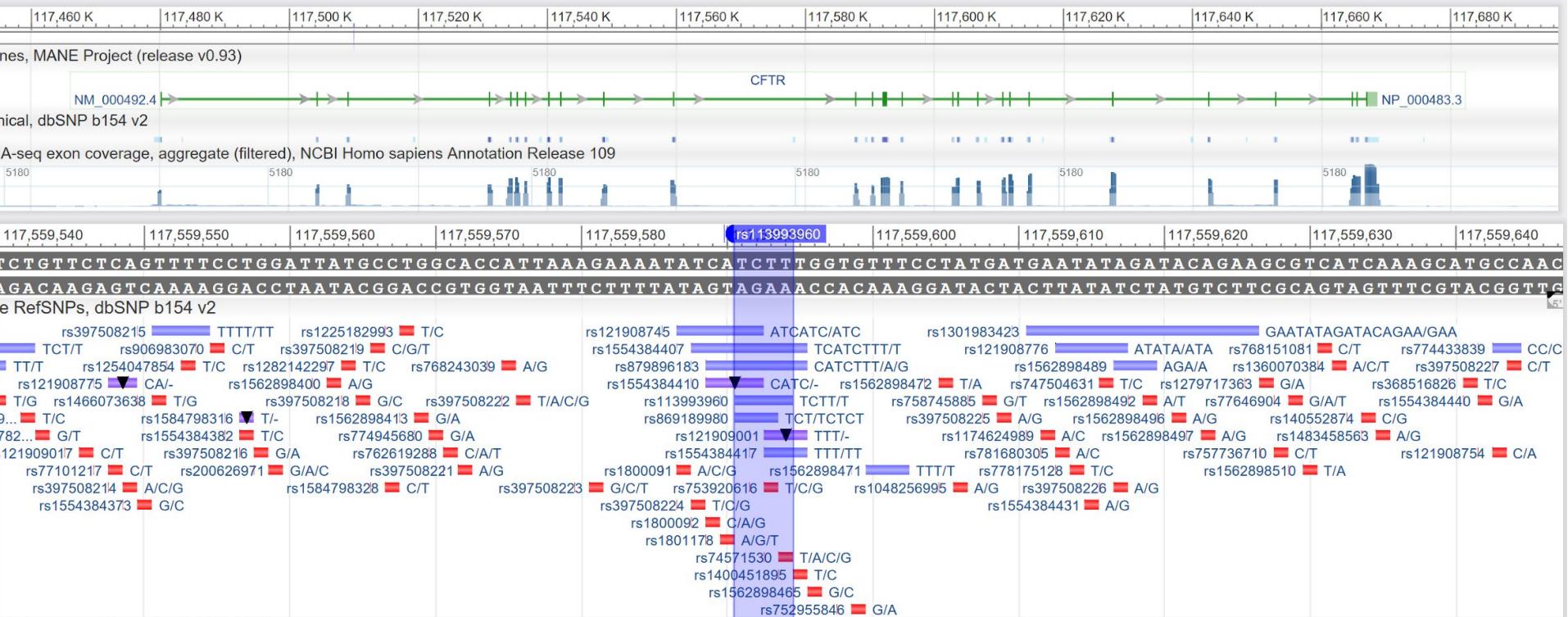



a

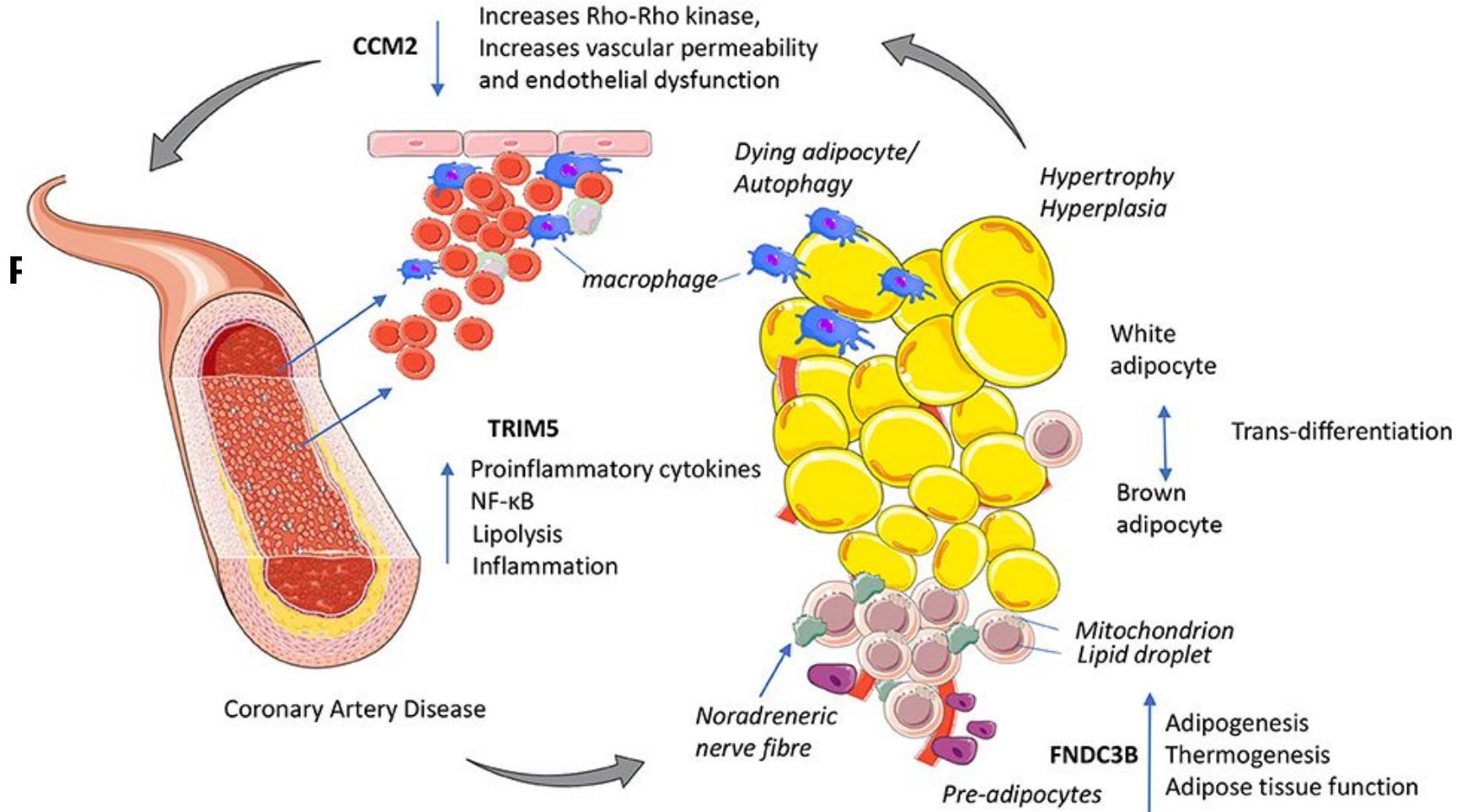
	CNV			Other SV (non-CNV)				Unresolved
SV class	Deletion	Duplication	Multiallelic CNV	Insertion	Inversion	Translocation	Complex SV	Breakends
Abbrev.	-DEL	-DUP	-MCNV	-INS	-INV	-CTX	-CPX	-BND
Ref.								
Example alternatives								
							(See Fig. 2)	Discarded



Cystic fibrosis

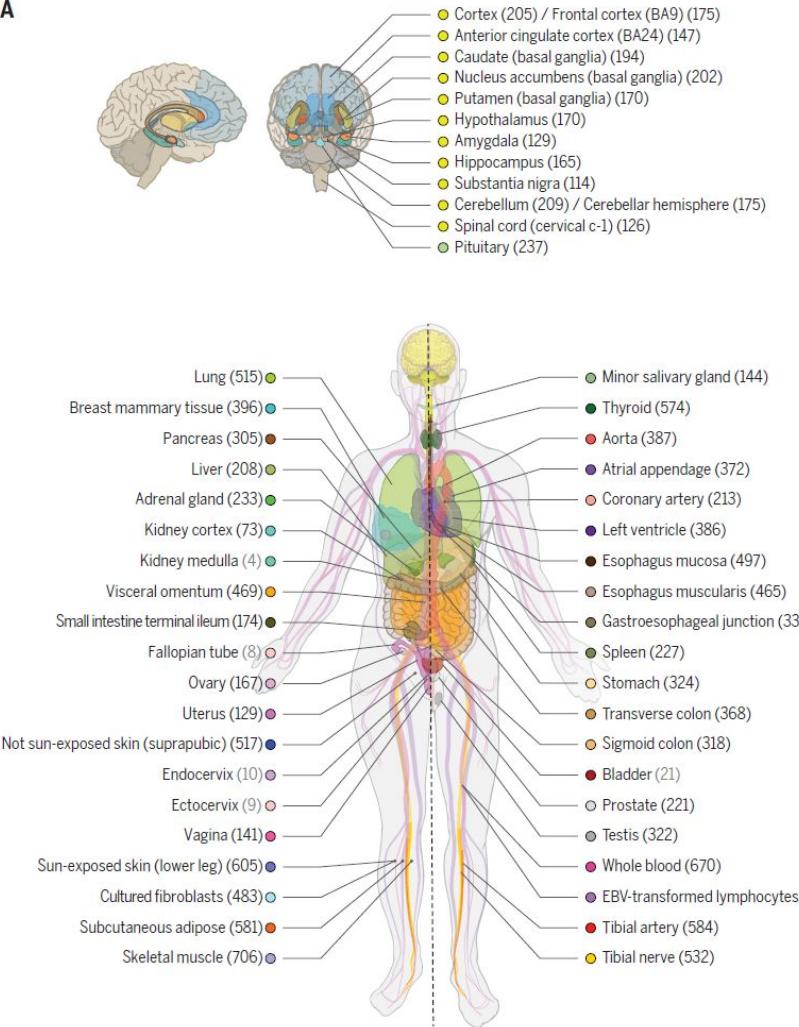


The *CFTR* gene (Chr 7), and rs113993960, the most common cause of CF



Dna Se

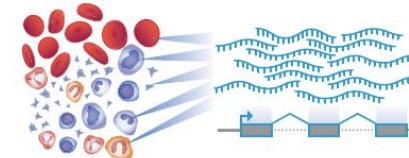
A



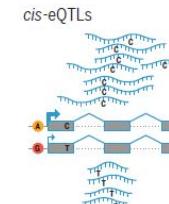
1

Cell type composition in tissues

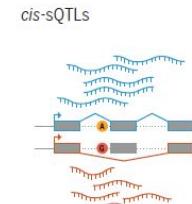
Gene expression and splicing



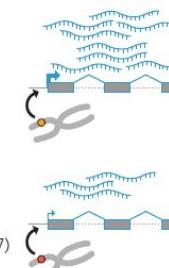
Expression quantitative trait loci (eQTLs)



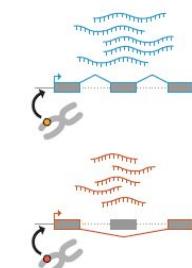
Splicing quantitative trait loci (sQTLs)



trans- α OTU



trans-sOTU



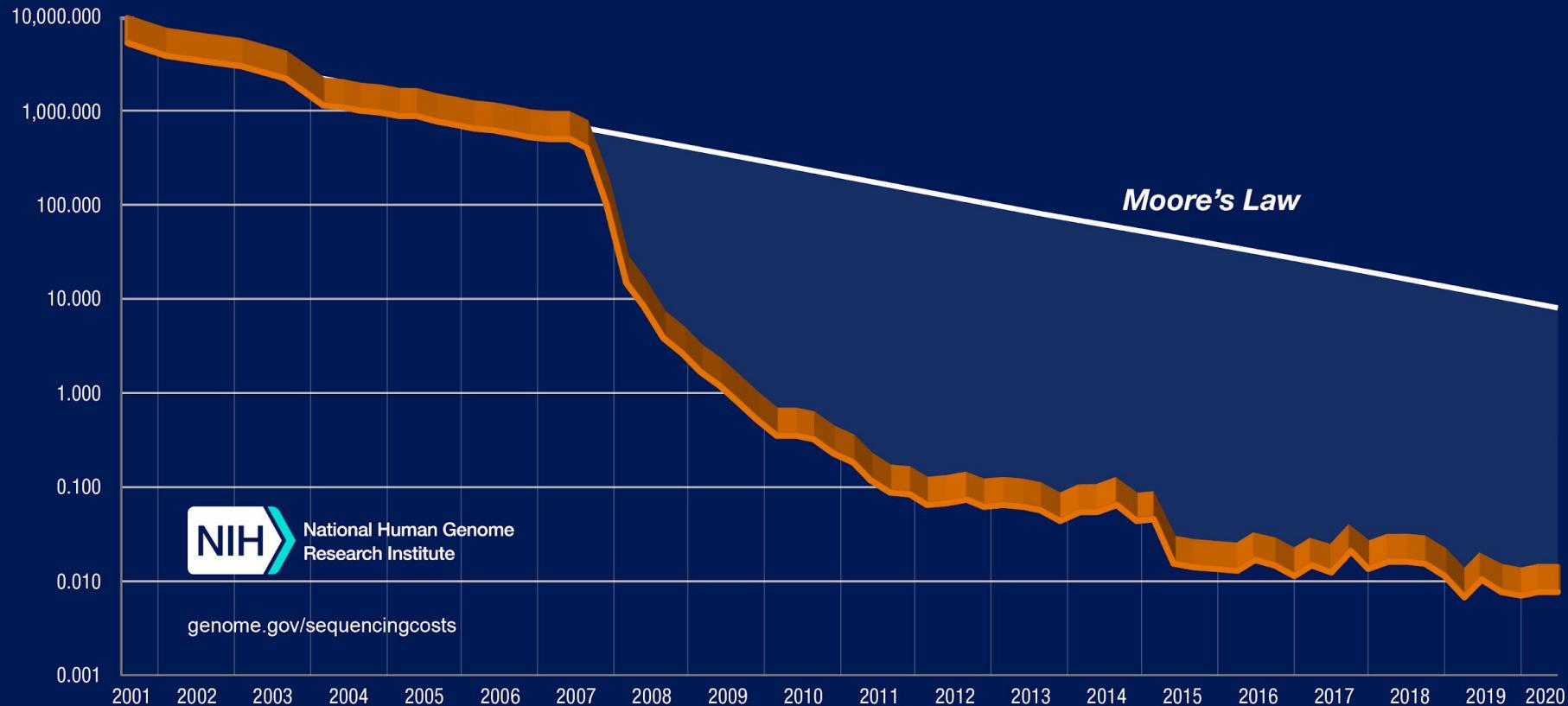
GTEX (v8)



National Human Genome Research Institute

FACT SHEETS
genome.gov

Cost per Raw Megabase of DNA Sequence



National Human Genome
Research Institute

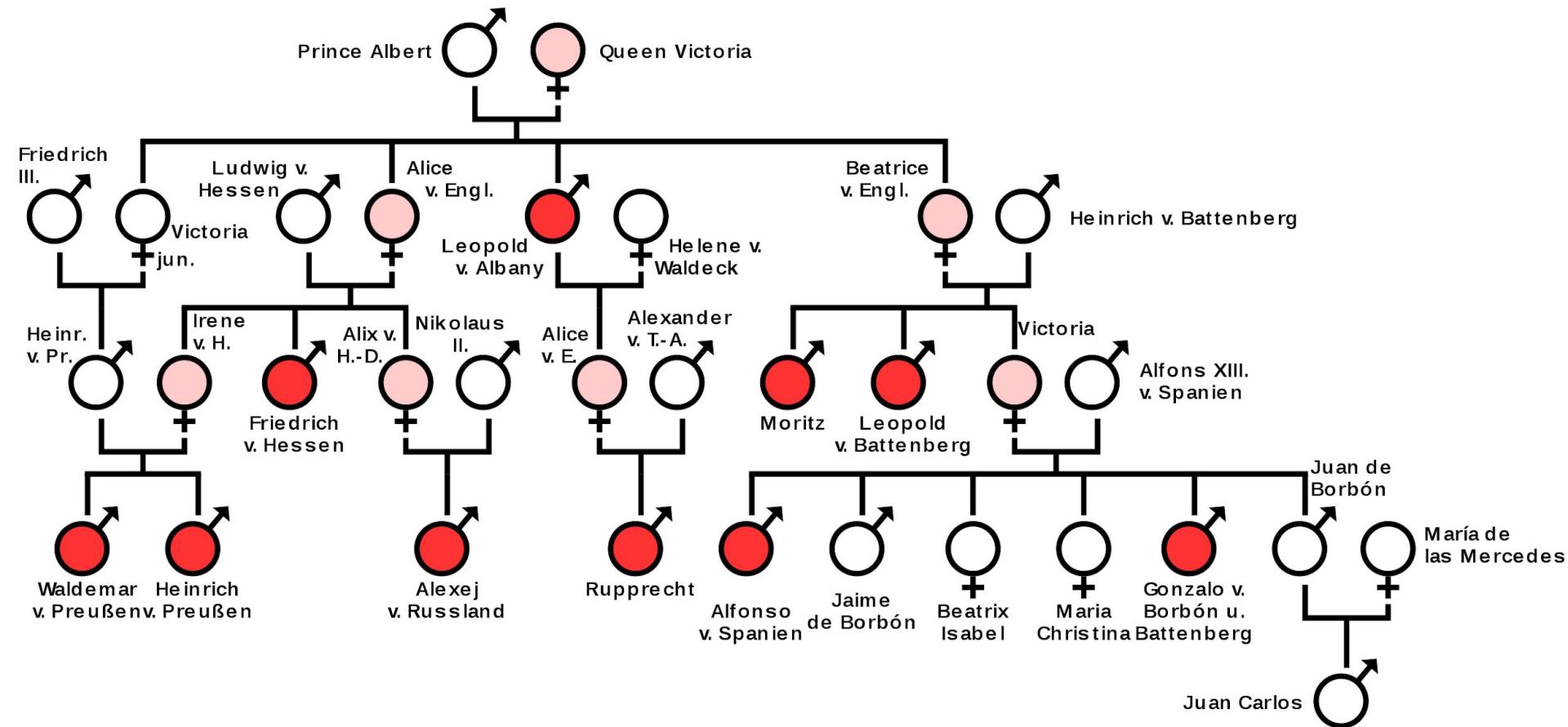
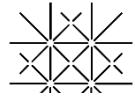
genome.gov/sequencingcosts

Cost per Human Genome



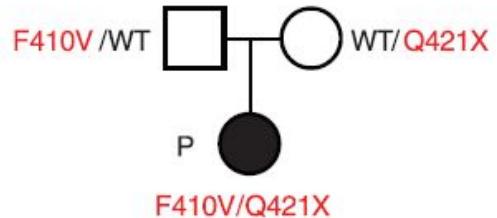


Haemophilia in the descendants of Queen Victoria

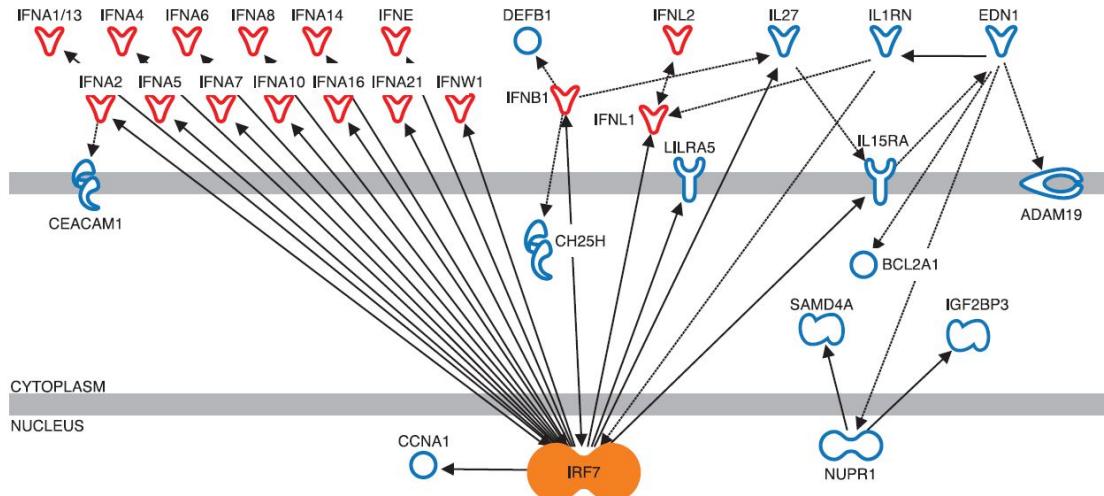
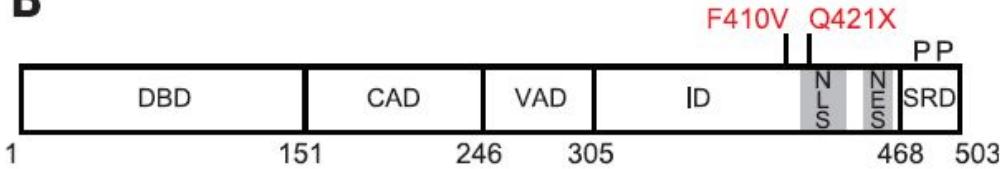


Life-threatening influenza infection in human IRF7 deficiency detected by trio sequencing

A



B



Exercise of *inference* (I)

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2 which is pending regulatory agency's review. The test has been shown to have a sensitivity of 99% and a specificity of 99%.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. Assume that 5% of the population is in fact infected. Was is your guess about the probability that Fred is indeed infected?

(Sensitivity is predicted true positive divided by all true positive; specificity is predicted true negative divided by all true negative).

Exercise of *inference* (I) - variants

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2 which is pending regulatory agency's review. When test with 100 SARS-Cov-2 patients, 99 report positive and one reports negative. When test with 100 healthy volunteers, 99 report negative and one reports positive.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. There are 30,000 people in the city where Fred lives; among them 1,500 are infected with SARS-Cov-2. What is the likelihood that Fred is truly infected given his positive test?

Exercise of *inference* (II)

Let's play a game! (The credit goes to David MacKay)

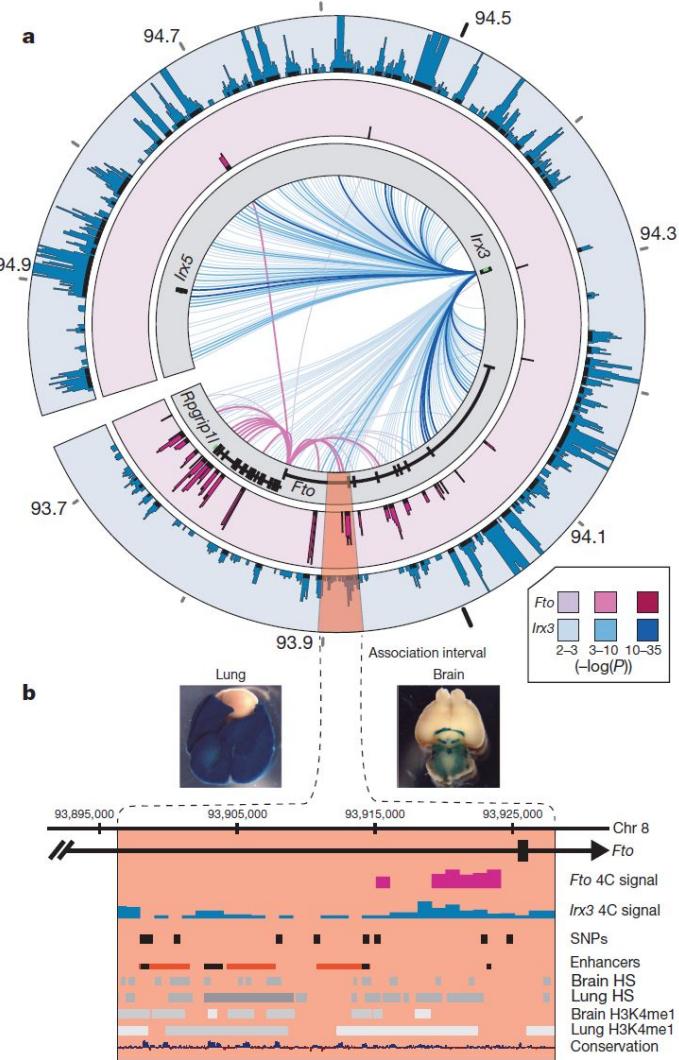
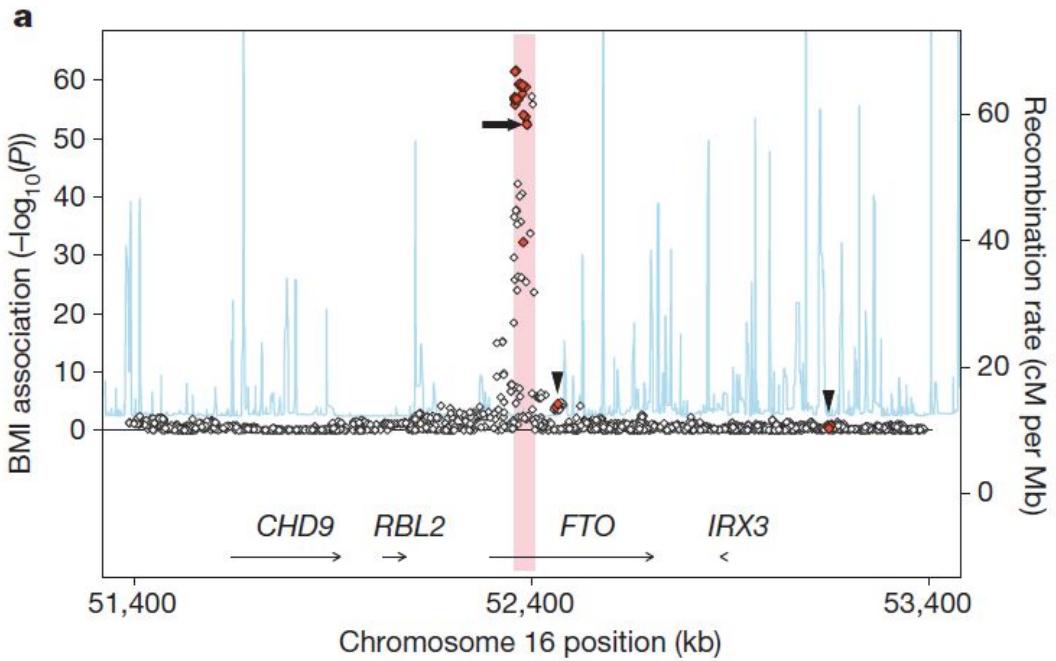
Exercise of *inference* (III)

- Cao and Moult (BMC Genomics, 2014) reported studied overlap between drug targets and GWAS hits.
- Use the data in the Table 1 of the paper ([cloned here](#)) to answer following the following two questions:
 - a. Assuming we know *nothing* about a gene (let's call it gene *WKN1*), what is the probability that the gene is a target for a disease listed here?
 - b. Assuming that we know nothing about another gene *WKN2* but that it is a GWAS hit for a disease, what is the probability that *WKN2* is a target for that disease?

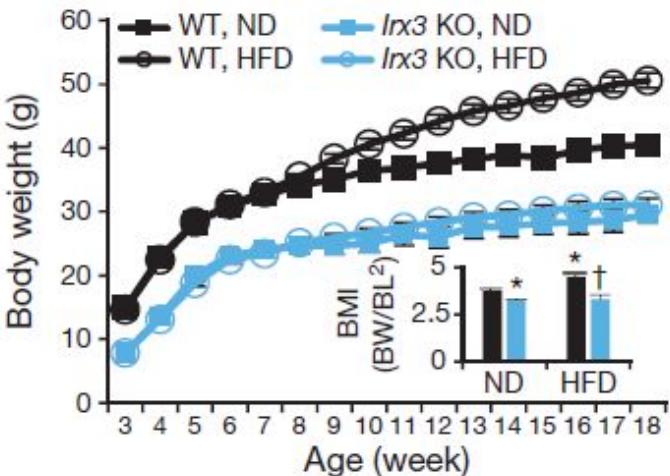
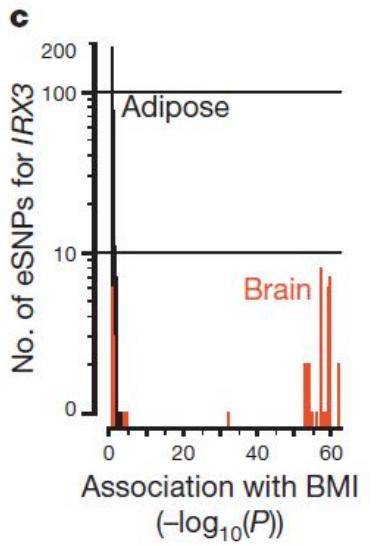
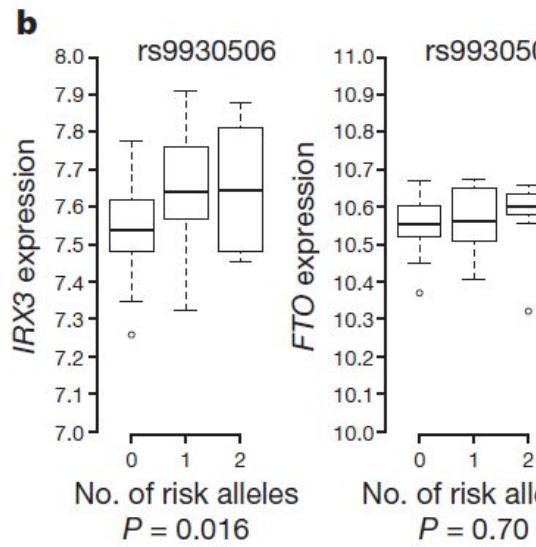
Discussion

What are other issues about using GWAS hits as drug targets?

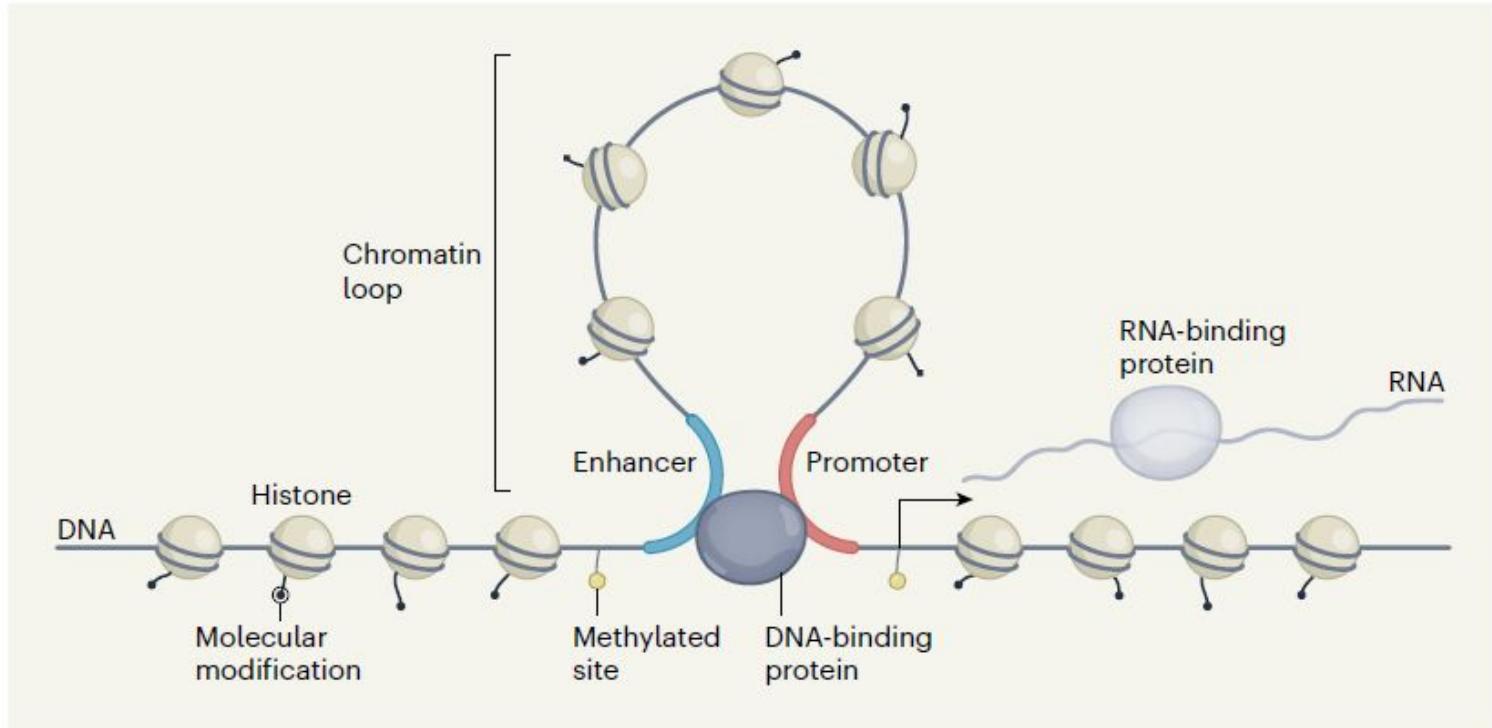
Is FTO a good target for obesity?



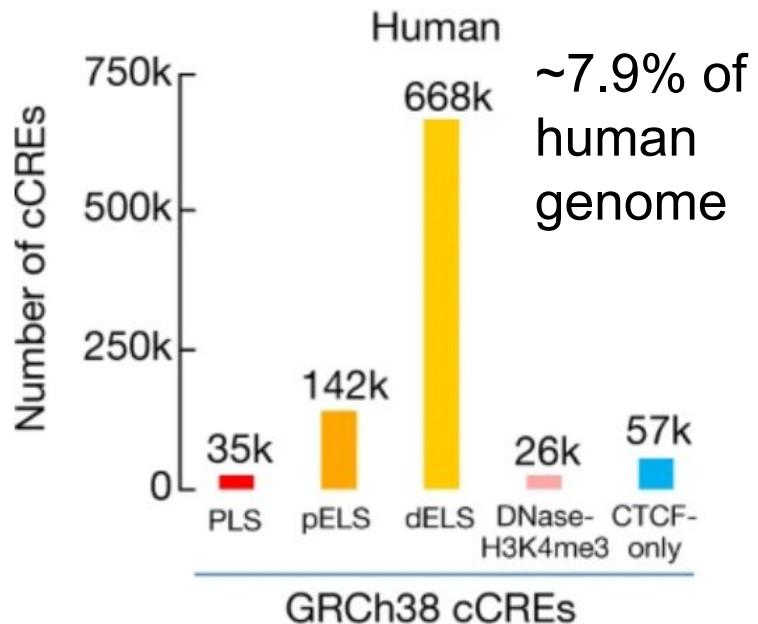
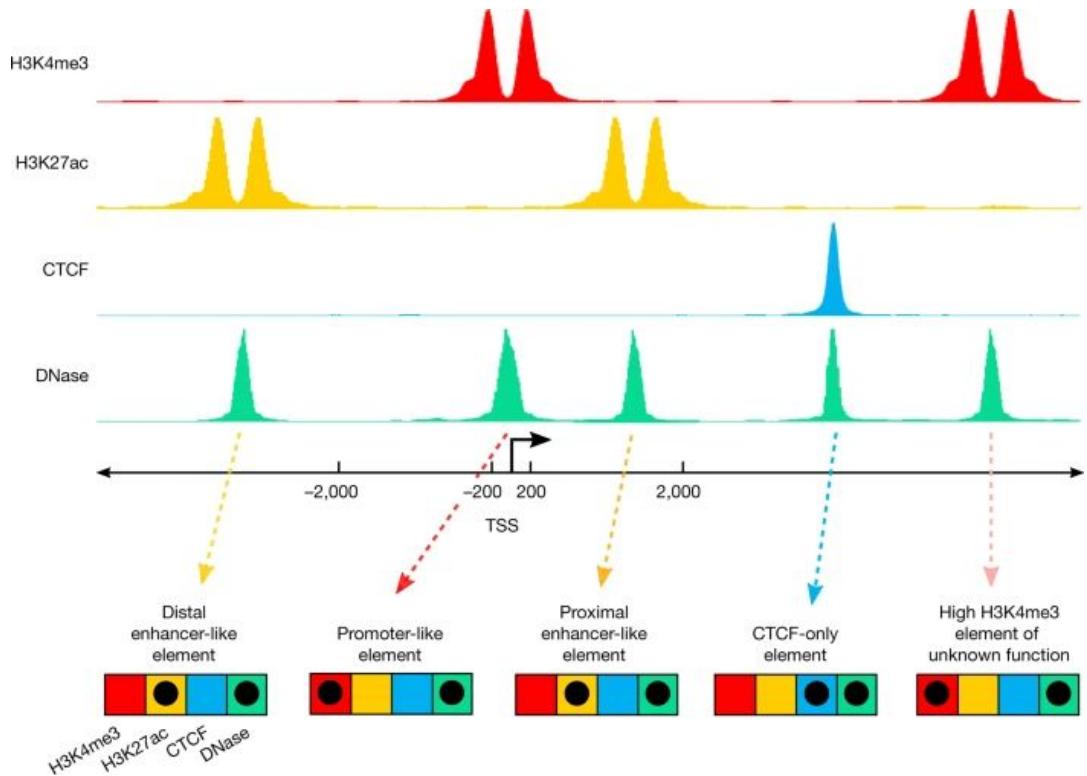
If at all, IRX3 is a more probable target



Much of the non-coding genome is junk, some is regulatory

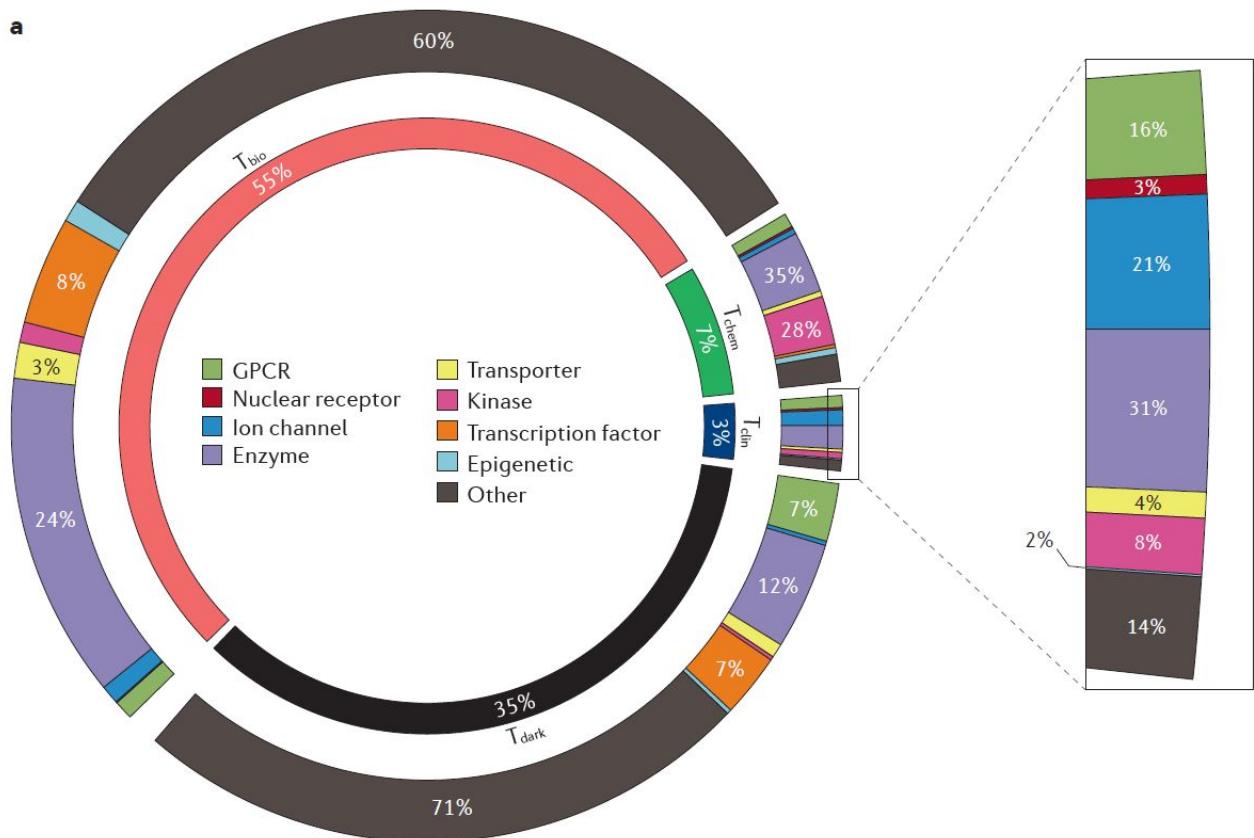
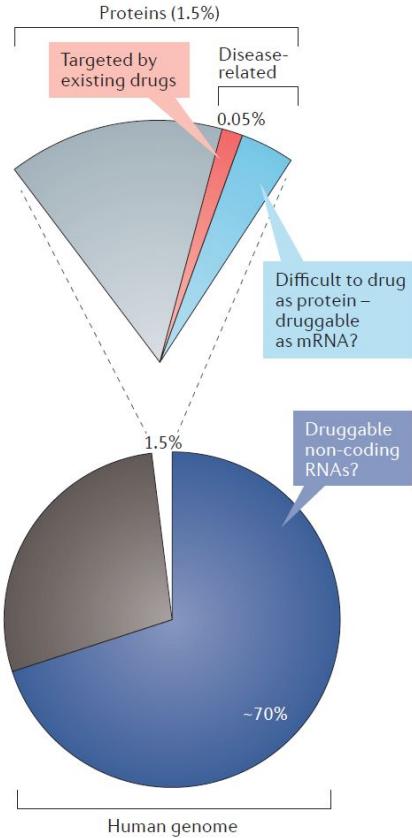


Candidate cis-regulatory elements (cCRE)

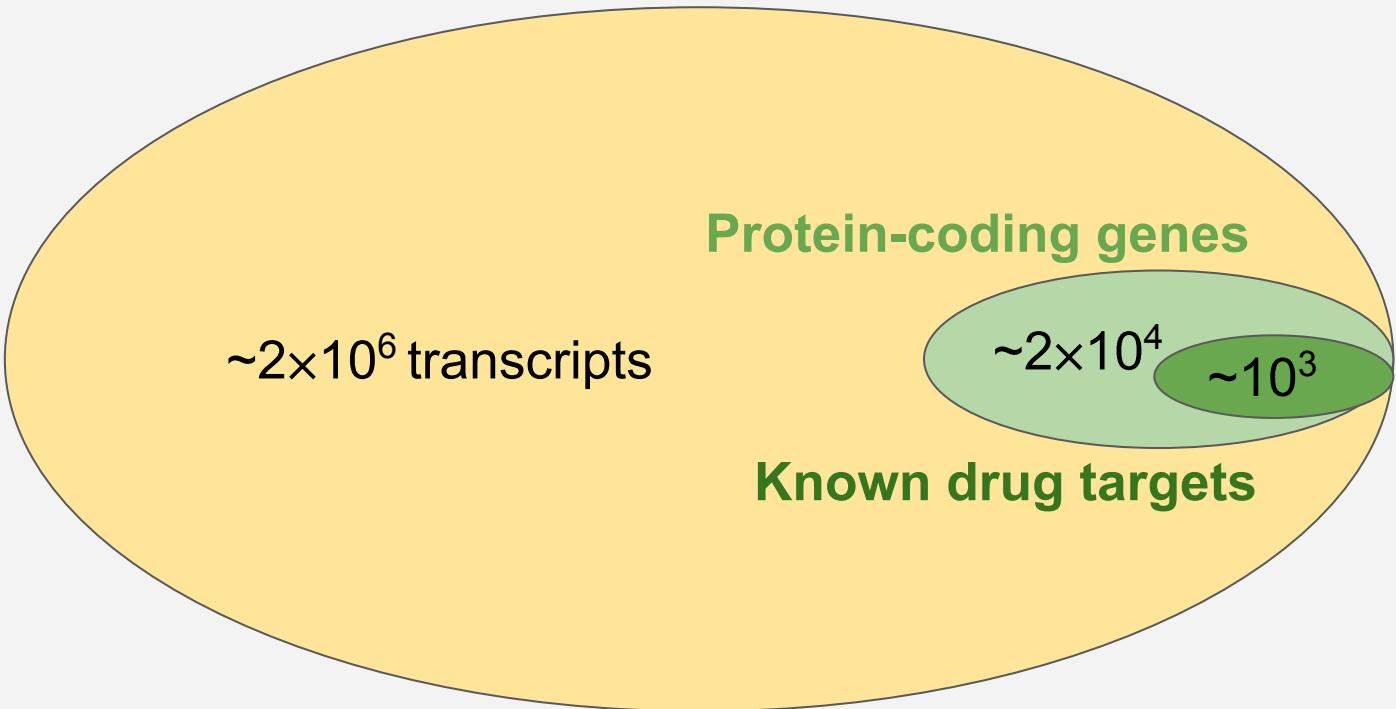


<https://screen.encodeproject.org/>

Challenge #1: little experience for much of the genome

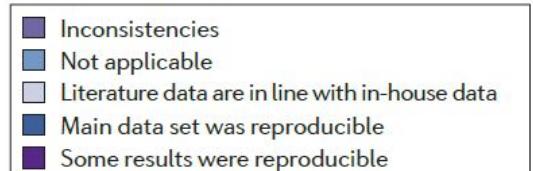
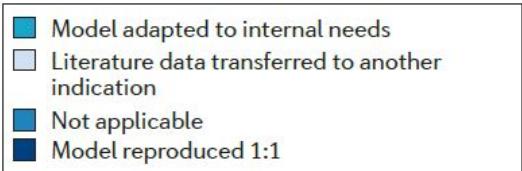
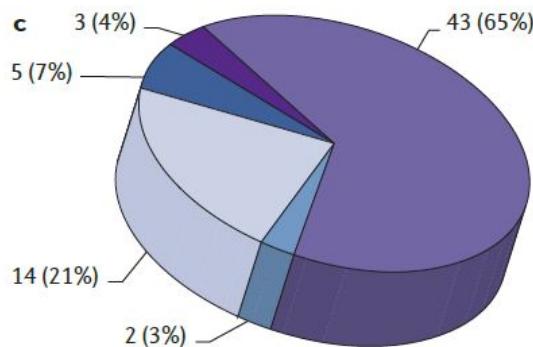
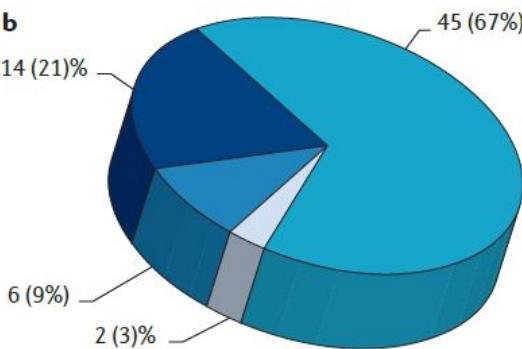
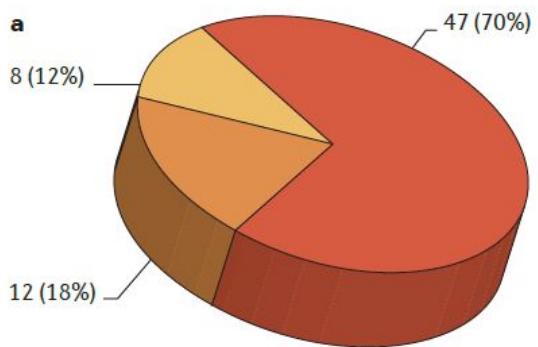


Protein, RNA, or DNA as target?



$\sim 3 \times 10^9$ DNA bases from maternal and paternal each

Challenge #2: Lack of reproducibility

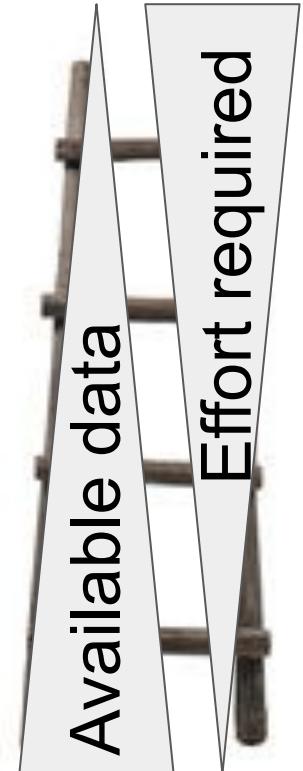


d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Challenge #3: The Target Ladder

3. [Real-world test] What would happen if we inhibit the activity of the kinase domain in the *WKN3* gene in patients with Alzheimer's Disease?
2. [Intervention] What would happen to human cells or to a rat model if we inhibit the activity of the kinase domain in the *WKN3* gene?
1. [Association] What are the evolutionary conservation, sequence, expression profile, expression regulation patterns, ... of the *WKN3* gene?



Conclusions

- Genomics and genetics offer unprecedented opportunities and challenges for target identification and assessment;
- Target identification and assessment involves knowledge integration and experimental validation;
- A central task of mathematical and computational biology in drug discovery is to perform inference, i.e. using information to reduce uncertainty.

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